changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising: (a) comparing said measured biological response profile to a library of artifact signatures to generate an artifact template, each of said artifact signatures comprising changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables, said artifact template comprising an artifact signature having greatest similarity to said biological response profile, said comparing comprising pattern matching of said measured biological response profile against said library; and (b) subtracting said artifact template from said measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.

REMARKS

Claims 58-64 and 70-76 were pending in the present application. Claims 58 and 71-72 have been amended to clarify the present invention. Applicants submit that entry of the amendments presented herein is proper in that the amendments place the claims in condition for allowance or place the case in better condition for appeal. In particular, Applicants respectfully submit that the amendments are made in response to the Examiner's rejections based on a newly made contention that "the labeling of the chromosomes is a perturbation which is biologically responded to by binding of said labeling material." Upon entry of the above-made amendments, claims 58-64 and 70-76 will be pending in the present application. A marked version showing changes made to the amended claims is attached hereto as Exhibit A. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Claims 58 and 71-72 have been amended to clarify that in the claimed methods, the measured biological response profile comprises measurements of a plurality of cellular constituents *of a living cell or organism*[1] *in response to a perturbation to said living cell or organism*. Support for the amendments is found in the specification at page 10, lines 17-20; page 12, lines 14-21; and the Example at pages 66-74.

No new matter has been added by these amendments. Entry of the foregoing amendments and the following remarks are respectfully requested.

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[1] Of course, as would be clear to a skilled artisan, the measurements of cellular constituents may be obtained when the cell is no longer alive.

EAR EI. SUM OK 1-25-02

APPLICANTS' INTERVIEW SUMMARY

Applicants thank Primary Examiner Ardin Marschel for the courtesies extended during the telephone interview on January 25, 2002 (hereinafter "the Interview") with R. Douglas Bradley, Applicant Yudong He and Applicants' representatives Adriane M. Antler and Weining Wang. During the interview, the Examiner indicated that the amendments and remarks as presented in the draft Amendment faxed to the Examiner for review on January 23, 2002 (which are essentially the same as those set forth herein) would overcome the rejections in the instant Office Action. However, the Examiner believed that the amendments to the claims would introduce new issues such that the entry of the amendments would not be proper after a final office action. The Examiner suggested that a Request for Continued Examination (RCE) be filed with the Amendment, after which the Examiner would issue a Notice of Allowance.

CORRECTION OF DRAWINGS

The Examiner has indicated that Applicants are required to submit drawing corrections within the time period set for responding to the Office Action. Applicants submit herewith formal drawings consisting of 27 sheets of drawings corresponding to Figures 1-20.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 58-64 and 70-76 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner contends that the phrase "an artifact pattern comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values" in claims 58 and 71-78 contains new matter "due to broadening the invention compared to the written basis as filed." The Examiner further contends that "[t]his broadening is directed to deviation in experimental values inclusive now of measurement artifacts as well as deviations caused by experimental values being the original conditions prior to measurement" and that "the artifacts are only disclosed as being caused by poor

control of RNA concentration which is an original condition deviation." Applicants respectfully disagree with the Examiner for reasons set forth below.

At the outset, Applicants respectfully submit that it is unclear as to what the Examiner categorizes as the "original conditions prior to measurement." Applicants construe the phrase in its plain meaning, i.e., conditions on the biological sample, e.g., cells, before the measurement process begins. Since the measurement process as commonly accepted in the art commences with the killing of the cells, e.g., for extraction of RNAs, Applicants surmise that the "original conditions prior to measurement" refer to conditions applied on the living cells, whereas "experimental values inclusive now of measurement artifact" refer to conditions applied during the measurement process after cells have been killed. Applicants base the following arguments on this construction of the Examiner's basis for his contentions.

Applicants respectfully submit that the disclosure in the specification as originally filed does not limit the invention to artifacts that are "deviations caused by experimental values being the original conditions prior to measurement." Applicants respectfully direct the attention of the Examiner to the specification at page 34, lines 25-32, which discloses that:

> [f]requently, when such profile data are obtained *there are one or more poorly controlled variables which lead to measured patterns of cellular constituents* (*e.g.*, measured gene expression patterns) which are, in fact, *artifacts of the measurement process* and are not part of the actual biological state or response (such as a perturbation response) being measured. Exemplary variables which may produce artifacts in biological profile data include, but are by no means limited to, cell culture density and temperature and hybridization temperature, as well as concentrations of total RNA and/or hybridization reagents. (emphasis added)

Thus, the specification does not distinguish and exclude artifacts that are "deviation[s] in experimental values inclusive now of measurement artifacts" from artifacts that are "deviations caused by experimental values being the original conditions prior to measurement." Quite to the contrary, the artifacts of the specification and the pending claims are "artifacts of the measurement process [that] are not part of the actual biological state or response" that arise due to "one or more poorly controlled variables which lead to measured patterns of cellular constituents" (specification at page 34, lines 25-29). Applicants further point out that, of the listed exemplary variables disclosed in the specification whose deviation may produce artifacts, such as cell culture density, temperature, hybridization temperature, and concentrations of hybridization reagents (see specification at page 34, lines 29-32), some

can be categorized as original conditions, e.g., cell culture density, whereas some are unambiguously part of the measurement process, e.g., hybridization temperature and concentration of hybridization reagents. With respect to the Examiner's allegation that the example in the specification on page 74, lines 8-32, shows that "the artifacts are only disclosed as being caused by poor control of RNA concentration which is an original condition deviation," Applicants respectfully point out that poor control of RNA concentration, as occurred in the step of reverse transcription after the cells were broken and RNA molecules had been extracted, *is* part of the measurement process.

Therefore, Applicants respectfully submit that the claims as amended are fully supported by the specification as originally filed, and no new matter has been added; and that the rejection under 35 U.S.C. § 112, first paragraph, is erroneous, and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102(e) SHOULD BE WITHDRAWN

Claim 58 is rejected under 35 U.S.C. § 102(e) as being anticipated by Garini et al., U.S. Patent No. 5,798,262 ("Garini"). In particular, the Examiner contends that "the labeling of the chromosomes is a perturbation which is biologically responded to by binding of said labeling material."

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

Applicants have amended claim 58 to more particularly point out that in the claimed method, the measured biological response profile comprises measurements of a plurality of cellular constituents *of a living cell or organism in response to a perturbation to said living cell or organism*. Garini discloses a method for classification of *in situ* painted chromosomes into a color karyotype and a method for identifying prominent internal reference spectra to effect such classification. In Garini, labeling with fluorophores is carried out on such spread chromosomes. For example, in Garini, "... 24 chromosome paints ... *were* simultaneously *hybridized with human mitotic chromosome spreads* ...." (Garini, col. 19, lines 19-33;

emphasis added). Applicants note that it is well known in the art that a metaphase chromosome spread is prepared by disrupting the cell and nucleus (thus killing the cell), and allowing the the metaphase chromosomes to spread on a surface. Applicants respectfully point out that, even if *arguendo*, the labeling of spread chromosomes is deemed a perturbation, it is a perturbation to the spread chromosomes rather than a perturbation to a living cell or organism and, as such, the obtained images of chromosomes are not measured biological response profiles comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to the living cell or organism. Nowhere does Garini teach a measured *biological response profile* which comprises measurements of a plurality of cellular constituents of a living cell or organism *in response to a perturbation to said living cell or organism* or an artifact which comprises *changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values*, much less a method of removing one or more such artifacts from such a measured biological response profile. Therefore, Applicants submit that Garini clearly does not anticipate the method of claim 58 of the present invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (e) over Garini be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)
SHOULD BE WITHDRAWN

Claims 58-64 and 70-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,798,262 ("Garini"). In particular, the Examiner contends that "the labeling of the chromosomes is a perturbation which is biologically responded to by binding of said labeling material." The Examiner also contends that Applicants' argument that Garini does not remove one or more artifacts from the measured response profile as presented in the Amendment filed on August 14, 2001 is non-persuasive. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable

expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants have amended claims 58 and 71-72 to more particularly point out that in the claimed method, the measured biological response profile comprises measurements of a plurality of cellular constituents *of a living cell or organism in response to a perturbation to said living cell or organism*. As discussed above, Garini discloses a method for classification of *in situ* painted chromosomes into a color karyotype and a method for identifying prominent internal reference spectra to effect such classification. In Garini, labeling with fluorophores is carried out on such spread chromosomes. For example, in Garini, "... 24 chromosome paints ... *were* simultaneously *hybridized with human mitotic chromosome spreads* ...." (Garini, col. 19, lines 19-33; emphasis added). Applicants note that it is well known in the art that a metaphase chromosome spread is prepared by disrupting the cell and nucleus (thus killing the cell), and allowing the the metaphase chromosomes to spread on a surface. Applicants respectfully point out that, even if *arguendo*, the labeling of spread chromosomes is deemed a perturbation, it is a perturbation to the spread chromosomes rather than a perturbation to a living cell or organism and, as such, the obtained images of chromosomes are not measured biological response profiles comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to the living cell or organism.

With respect to the Examiner's contention that Applicants' argument presented in the Amendment filed on August 14, 2001 is non-persuasive, Applicants respectfully point out that in the methods disclosed in Garini, an obtained karyotype is compared to reference spectra. It is clear to one of skill in the art that the reference spectra used in these methods are intrinsic characteristics of chromosomes and are not *changes in measurements* of cellular constituents *resulting from deviation of one or more experimental variables from desired values*. It is also clear to one of skill in the art that in Garini, matching an obtained karyotype to reference spectra is for classification of the obtained karyotype rather than for removal of the reference spectra from the karyotype.

Therefore, Garini fails to provide any hint or suggestion of the claimed invention. Garini does not teach or suggest a measured biological response profile which comprises measurements of a plurality of cellular constituents of a living cell or organism *in response to a perturbation to the living cell or organism*. Garini does not teach or suggest an artifact

which comprises *changes in measurements* of cellular constituents *resulting from deviation of one or more experimental variables from desired values*. Garini does not teach or suggest removing one or more such artifacts from a measured biological response profile which comprises measurements of a plurality of cellular constituents of a living cell or organism *in response to a perturbation to said living cell or organism*. Garini does not teach or suggest an artifact template which comprises an artifact signature which has greatest similarity to the measured biological response profile, or teach or suggest obtaining such an artifact signature by comparing the measured biological response profile to a library of artifact signatures, each comprising changes in amplitudes of measurements of the cellular constituents corresponding to different levels of the one or more experimental variables. Nor does Garini teach or suggest a method for removing one or more artifacts from a measured biological response profile by subtracting an artifact template from the measured biological response profile. One of ordinary skill in the art would not be motivated to such methods with a reasonable expectation of success from the teachings of Garini. Therefore, the presently claimed invention is not made obvious by the cited reference. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition

for allowance. Withdrawal of the Examiner's rejections, and allowance of the application, are respectfully requested.

Respectfully submitted,

Date January 30, 2002

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Enclosures

EXHIBIT A: MARKED VERSION OF THE AMENDED CLAIMS
U.S. APPLICATION SERIAL NO. 09/220,275
(ATTORNEY DOCKET NO. 9301-039-999)

(as amended January 30, 2002)

58. (Three Times Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents [in] of a [biological sample] living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising an artifact pattern comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting said one or more artifact patterns from the measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.

71. (Twice Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents [in] of a [biological sample] living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting an artifact template from the measured biological response profile, wherein said artifact template comprises an artifact signature having greatest similarity to said biological response profile and is obtained by a method comprising comparing said measured biological response profile to a library of artifact signatures, each of said artifact signatures comprising changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables, said comparing comprising pattern matching of said measured biological response profile against said library; thereby removing said one or more artifacts from said measured biological response profile.

72. (Twice Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising

measurements of a plurality of cellular constituents [in] of a [biological sample] living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising: (a) comparing said measured biological response profile to a library of artifact signatures to generate an artifact template, each of said artifact signatures comprising changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables, said artifact template comprising an artifact signature having greatest similarity to said biological response profile, said comparing comprising pattern matching of said measured biological response profile against said library; and (b) subtracting said artifact template from said measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.